

ANTIBODY MOLECULES TO CD138 AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/566,936, filed October 2, 2017, and U.S. Provisional Application No. 62/725,880, filed August 31, 2018. The contents of the aforesaid applications are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on September 26, 2018, is named P2029-7017WO_SL.txt and is 171,304 bytes in size.

BACKGROUND

Multiple myeloma (MM) is a cancer formed by malignant plasma cells. These tumors generally develop in bone, but occasionally are found in other tissues. Disease with a single plasma cell tumor is known as an isolated (or solitary) plasmacytoma. When more than one plasmacytoma is present, it is known as multiple myeloma. In the United States, the estimated new cases are about 30,000 in 2017 and more than 10,000 deaths are expected to occur. Despite treatment advances in multiple myeloma therapy, multiple myeloma remains an incurable disease in most patients.

There is a need for developing new approaches for treating, preventing and diagnosing multiple myeloma and other disorders that share similar disease mechanisms.

SUMMARY

This disclosure provides, at least in part, antibody molecules that bind to CD138, *e.g.*, human CD138, and that comprise one or more functional and structural properties disclosed herein. In an example, the antibody molecule is capable of causing an effector function (*e.g.*, an antibody-dependent cellular cytotoxicity (ADCC) activity) on a cell expressing CD138. In an example, the antibody molecule preferentially binds to a membrane-bound CD138 versus a soluble CD138. In an example, the antibody molecule binds to an epitope in an extracellular region of CD138 that is proximal to the transmembrane domain. In an example, the antibody molecule does not bind to the integrin binding domain (IBD) of CD138. In an example, the antibody molecule does not bind exclusively to the IBD of CD138. While not wishing to be bound by theory, it is believed that in an example, improved or optimal cytotoxicity can be achieved, by targeting certain extracellular region(s) on membrane-bound CD138 that is proximal to the cell membrane.

In an example, the antibody molecule is selected from **Table 1**, or competes for binding to CD138 with an anti-CD138 monoclonal antibody selected from **Table 1**. In an example, the antibody molecule binds to the same or overlapping epitope as the epitope recognized by an anti-

CD138 monoclonal antibody selected from **Table 1**. In an example, the antibody molecule comprises one or more heavy chain variable regions and/or one or more light chain variable regions described in **Table 1**. In an example, the antibody molecule comprises one or more heavy chain CDRs and/or one or more light chain CDRs described in **Table 1**.

5 In an example, antibody molecule-drug conjugates (ADCs), nucleic acid molecules encoding the antibody molecules, expression vectors, host cells, compositions (*e.g.*, pharmaceutical compositions), kits, containers, and methods for making the antibody molecules, are also provided. The antibody molecules disclosed herein can be used (alone or in combination with other agents or therapeutic modalities) to treat, prevent and/or diagnose disorders associated with CD138, *e.g.*, cancer
10 or precancerous conditions (*e.g.*, multiple myeloma or smoldering myeloma).

Accordingly, in certain examples, this disclosure provides an antibody molecule, *e.g.*, an antibody molecule described herein, having one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or all) of the following properties a)-dd):

- 15 a) Binds to CD138 (*e.g.*, human CD138) with high affinity, *e.g.*, with a dissociation constant (K_D) of less than about 100 nM, typically about 10 nM, and more typically, about 10-0.001 nM, about 10-0.01 nM, about 5-0.01 nM, about 3-0.05 nM, about 1-0.1 nM, or stronger, *e.g.*, less than about 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM,
- 20 b) Binds to a membrane-bound CD138 with high affinity, *e.g.*, with a dissociation constant (K_D) of less than about 100 nM, typically about 10 nM, and more typically, about 10-0.001 nM, about 10-0.01 nM, about 5-0.01 nM, about 3-0.05 nM, about 1-0.1 nM, or stronger, *e.g.*, less than about 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM,
- 25 c) Binds to a soluble CD138 i) with high affinity, *e.g.*, with a dissociation constant (K_D) of less than about 100 nM, typically about 10 nM, and more typically, about 10-0.001 nM, about 10-0.01 nM, about 5-0.01 nM, about 3-0.05 nM, about 1-0.1 nM, or stronger, *e.g.*, less than about 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM; or ii) with low affinity, *e.g.*, with a dissociation constant (K_D) of
30 greater than about 100 nM, *e.g.*, greater than about 200, 300, 400, or 500 nM,
- d) Binds to a membrane-bound CD138, or an intact ectodomain of CD138, i) preferably over a soluble CD138, *e.g.*, the binding affinity to a membrane-bound CD138, or an intact ectodomain of CD138, is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold higher than the binding affinity to a soluble CD138; or ii) with a binding affinity similar to the binding affinity to a soluble CD138, *e.g.*, the binding affinity to a membrane-bound CD138, or an intact
35 ectodomain of CD138, is less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% higher than the binding affinity to a soluble CD138,

bb) Has one or more biological properties of an anti-CD138 monoclonal antibody described herein,

cc) Has one or more structural properties of an anti-CD138 monoclonal antibody described herein, or

5 dd) Has one or more pharmacokinetic properties of an anti-CD138 monoclonal antibody described herein.

In an example, this disclosure features an anti-CD138 antibody molecule, which: (i) binds, or substantially binds, to CD138 in an extracellular region proximal to the transmembrane domain of
10 CD138; and (ii) causes an antibody-dependent cellular cytotoxicity (ADCC) activity on a cell expressing CD138.

In an aspect, there is provided an anti-CD138 antibody molecule, which:

(i) binds to CD138 in an extracellular region proximal to the transmembrane domain of CD138; wherein the C-terminus of the extracellular region proximal to the transmembrane domain is
15 within 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain;

and/or wherein the N-terminus of the extracellular region proximal to the transmembrane domain is within 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain; and

20 (ii) causes an antibody-dependent cellular cytotoxicity (ADCC) activity on a cell expressing CD138.

In an example, the C-terminus of the extracellular region proximal to the transmembrane domain is within 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain. In an example, the N-terminus of the extracellular region
25 proximal to the transmembrane domain is within 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain.

In an example, the antibody molecule binds to an epitope on CD138 comprising five or more (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or more) consecutive amino acid residues in the extracellular region.

30 In an example, the extracellular region proximal to the transmembrane domain comprises, or consists of, amino acids 210-250 or 220-245 of any of SEQ ID NOS: 1-3 or 450.

In an example, the antibody molecule binds to an Fc receptor (FcR) (*e.g.*, one or more of FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, or FcγRIIIb) on the surface of an immune cell (*e.g.*, a natural killer (NK) cell, a macrophage, a monocyte, or an eosinophil).

35 In an example, the cell expressing CD138 is a cancer cell or precancerous cell. In an example, the cancer or precancerous cell is a myeloma cell.

In an example, the antibody molecule further binds, or binds with higher affinity, to an extracellular region of CD138 distant from the transmembrane domain. In an example, the antibody molecule binds to an epitope on CD138 comprising five or more (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, or more) consecutive amino acid residues in an extracellular region distant from the transmembrane domain. In an example, the C-terminus of the extracellular region distant from the transmembrane domain is at least 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 amino acids away from the N-terminus of the transmembrane domain. In an example, the extracellular region distant from the transmembrane domain comprises amino acids 23-50, 51-95, 88-121, or 111-150 of any of SEQ ID NOS: 1-3 or 450. In some examples, the extracellular region distant from the transmembrane domain comprises amino acids 88-121 or 101-121 of any of SEQ ID NOS: 1-3 or 450.

In an example, the antibody molecule further binds, or binds with higher affinity, to the integrin binding domain (IBD) of CD138. In an example, the antibody molecule further binds, or binds with high affinity, to a region N-terminal to the IBD of CD138.

In an example, the antibody molecule does not bind, or binds with low affinity, to an extracellular region of CD138 distant from the transmembrane domain. In an example, the antibody molecule does not bind to an epitope on CD138 comprising five or more (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, or more) consecutive amino acid residues in an extracellular region distant from the transmembrane domain. In an example, the C-terminus of the extracellular region distant from the transmembrane domain is at least 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 amino acids away from the N-terminus of the transmembrane domain. In an example, the extracellular region distant from the transmembrane domain comprises amino acids 23-50, 51-95, 88-121, or 111-150 of any of SEQ ID NOS: 1-3 or 450.

In an example, the antibody molecule does not bind, or binds with low affinity, to the integrin binding domain (IBD) of CD138. In an example, the antibody molecule does not bind, or binds with low affinity, to a region N-terminal to the IBD of CD138.

In an example, the antibody molecule binds to CD138 with a disassociation constant (K_D) of less than about 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or about 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM.

In an example, the binding affinity of the antibody molecule to a membrane-bound CD138 is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 200, or 500-fold higher than the binding affinity to a soluble CD138. In an example, the antibody molecule binds to a membrane-bound CD138 with a K_D less than about 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or about 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM.

In an example, the binding affinity of the antibody molecule to a membrane-bound CD138 is similar its binding affinity to a soluble CD138, *e.g.*, the binding affinity to a membrane-bound CD138 is within about $\pm 10\%$, $\pm 20\%$, $\pm 30\%$, $\pm 40\%$, $\pm 50\%$, $\pm 60\%$, $\pm 70\%$, $\pm 80\%$, $\pm 90\%$, $\pm 100\%$ of, *e.g.*, less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% higher than, the binding affinity to a soluble CD138. In an example, the antibody molecule binds to a soluble CD138 with a K_D of less than about 100 nM, typically about 10 nM, and more typically, about 10-0.001 nM, about 10-0.01 nM, about 5-0.01 nM, about 3-0.05 nM, about 1-0.1 nM, or stronger, *e.g.*, less than about 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM. In an example, the antibody molecule binds to a soluble CD138 with a K_D of greater than about 100, 200, 300, 400, or 500 nM.

In an example, the antibody molecule binds to a membrane-bound CD138 preferably over a soluble CD138, *e.g.*, the binding affinity to a membrane-bound CD138 is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold higher than the binding affinity to a soluble CD138. In an example, the antibody molecule binds to a soluble CD138 preferably over a membrane-bound CD138, *e.g.*, the binding

affinity to a soluble CD138 is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold higher than the binding affinity to a membrane-bound CD138. In an example, the antibody molecule binds to both soluble CD138 and to membrane-bound CD138.

In an example, the antibody molecule binds to C1q and causes a complement-dependent cytotoxicity (CDC) activity on a cell expressing CD138. In an example, the antibody molecule reduces (*e.g.*, inhibits, blocks, or neutralizes) one or more biological activities of a cell expressing CD138 *in vitro*, *ex vivo*, or *in vivo*. In an example, the antibody molecule mediates homotypic adhesion of one or more CD138-expressing cells. In an example, the antibody molecule inhibits the action of a protease on a membrane-bound CD138, *e.g.*, to reduce shedding of CD138. In an example, the antibody molecule reduces (*e.g.*, inhibits) proliferation of a cancer or precancerous cell expressing CD138.

In an example, the antibody molecule comprises one or more (*e.g.*, two or three) heavy chain CDRs and/or one or more (*e.g.*, two or three) light chain CDRs of an anti-CD138 monoclonal antibody described herein. In an example, the antibody molecule comprises a heavy chain variable region (VH) and/or light chain variable region (VL) of an anti-CD138 monoclonal antibody described herein. In an example, the antibody molecule comprises an Fc region.

In an example, the disclosure features an anti-CD138 antibody molecule, which binds, or substantially binds, to an epitope on CD138 comprising four or more (*e.g.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or more) consecutive amino acid residues in an extracellular region proximal to the transmembrane domain of CD138.

In an example, the C-terminus of the extracellular region proximal to the transmembrane domain is within 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain. In an example, the N-terminus of the extracellular region proximal to the transmembrane domain is within 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain. In an example, the extracellular region proximal to the transmembrane domain comprises, or consists of, amino acids 176-250 of any of SEQ ID NOS: 1-3 or 450.

In an example, the antibody molecule binds to an Fc receptor (FcR) (*e.g.*, one or more of FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, or FcγRIIIb) on the surface of an immune cell (*e.g.*, a natural killer (NK) cell, a macrophage, a monocyte, or an eosinophil). In an example, the antibody molecule is capable of causing (*e.g.*, promoting or inducing) an ADCC activity on a cell expressing CD138. In an example, the antibody molecule is capable of causing (*e.g.*, promoting or inducing) antibody dependent cellular phagocytosis (ADCP) activity on a cell expressing CD138. In an example, the cell expressing CD138 is a cancer cell or precancerous cell. In an example, the cancer or precancerous cell is a myeloma cell.

In an example, the antibody molecule further binds, or binds with higher affinity, to an extracellular region of CD138 distant from the transmembrane domain. In an example, the antibody molecule binds to an epitope on CD138 comprising five or more (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, or more) consecutive amino acid residues in an extracellular region distant from the transmembrane domain. In an example, the C-terminus of the extracellular region distant from the transmembrane domain is at least 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 amino acids away from the N-terminus of the transmembrane domain. In an example, the extracellular region distant from the transmembrane domain comprises amino acids 23-50, 51-95, 88-121, or 111-150 of any of SEQ ID NOS: 1-3 or 450.

In an example, the antibody molecule further binds, or binds with higher affinity, to the integrin binding domain (IBD) of CD138. In an example, the antibody molecule further binds, or binds with high affinity, to a region N-terminal to the IBD of CD138.

In an example, the antibody molecule does not bind, or binds with low affinity, to an extracellular region of CD138 distant from the transmembrane domain.

In an example, the epitope does not comprise five or more (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, or more) consecutive amino acid residues in an extracellular region distant from the transmembrane domain. In an example, the C-terminus of the extracellular region distant from the transmembrane domain is at least 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 amino acids away from the N-terminus of the transmembrane domain. In an example, the extracellular region distant from the transmembrane domain comprises amino acids 23-50, 51-95, 88-121, or 111-150 of any of SEQ ID NOS: 1-3 or 450.

In an example, the antibody molecule does not bind, or binds with low affinity, to the integrin binding domain (IBD) of CD138. In an example, the antibody molecule does not bind, or binds with low affinity, to a region N-terminal to the IBD of CD138.

In an example, the antibody molecule binds to CD138 with a disassociation constant (K_D) of less than about 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or about 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM.

In an example, the binding affinity of the antibody molecule to a membrane-bound CD138 is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 200, or 500-fold higher than the binding affinity to a soluble CD138. In an example, the antibody molecule binds to a membrane-bound CD138 with a K_D less than about 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or about 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM. In an example, the antibody molecule binds to a soluble CD138 with a K_D of greater than about 100, 200, 300, 400, or 500 nM.

In an example, the binding affinity of the antibody molecule to a membrane-bound CD138 is similar its binding affinity to a soluble CD138, *e.g.*, the binding affinity to a membrane-bound CD138 is within about $\pm 10\%$, $\pm 20\%$, $\pm 30\%$, $\pm 40\%$, $\pm 50\%$, $\pm 60\%$, $\pm 70\%$, $\pm 80\%$, $\pm 90\%$, $\pm 100\%$

of, *e.g.*, less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% higher than, the binding affinity to a soluble CD138. In an example, the antibody molecule binds to a soluble CD138 with a K_D of less than about 100 nM, typically about 10 nM, and more typically, about 10-0.001 nM, about 10-0.01 nM, about 5-0.01 nM, about 3-0.05 nM, about 1-0.1 nM, or stronger, *e.g.*, less than about 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM. In an example, the antibody molecule binds to a soluble CD138 with a K_D of greater than about 100, 200, 300, 400, or 500 nM.

In an example, the antibody molecule binds to a membrane-bound CD138 preferably over a soluble CD138, *e.g.*, the binding affinity to a membrane-bound CD138 is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold higher than the binding affinity to a soluble CD138. In an example, the antibody molecule binds to a soluble CD138 preferably over a membrane-bound CD138, *e.g.*, the binding affinity to a soluble CD138 is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold higher than the binding affinity to a membrane-bound CD138. In an example, the antibody molecule binds to both soluble CD138 and to membrane-bound CD138.

In an example, the antibody molecule binds to C1q and causes a complement-dependent cytotoxicity (CDC) activity on a cell expressing CD138. In an example, the antibody molecule reduces (*e.g.*, inhibits, blocks, or neutralizes) one or more biological activities of a cell expressing CD138 *in vitro*, *ex vivo*, or *in vivo*. In an example, the antibody molecule mediates homotypic adhesion of one or more CD138-expressing cells. In an example, the antibody molecule inhibits the action of a protease on a membrane-bound CD138, *e.g.*, to reduce shedding of CD138. In an example, the antibody molecule reduces (*e.g.*, inhibits) proliferation of a cancer or precancerous cell expressing CD138.

In an example, the antibody molecule comprises one or more (*e.g.*, two or three) heavy chain CDRs and/or one or more (*e.g.*, two or three) light chain CDRs of an anti-CD138 monoclonal antibody described herein. In an example, the antibody molecule comprises a heavy chain variable region (VH) and/or light chain variable region (VL) of an anti-CD138 monoclonal antibody described herein. In an example, the antibody molecule comprises an Fc region.

In an example, the disclosure features an anti-CD138 antibody molecule comprising one or both of:

(a) a heavy chain variable region (VH), wherein the VH comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3), wherein the VH comprises one, two, or all of the following: (i) an HCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the HCDR1 of an anti-CD138 monoclonal antibody described herein (*e.g.*, any of antibodies CD001, CD002, CD003, CD004, CD005, CD006, 602, 603, 604, 607, 613, 614, 617, 624, 632, 616, 619, 623, 1610, 2510, 2610, 2710, 2810, 2910, or 1409); (ii) an HCDR2

comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the HCDR2 of the anti-CD138 antibody; or (iii) an HCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the HCDR3 of the anti-CD138 antibody; or

(b) a light chain variable region (VL), wherein the VL comprises three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), wherein the VL comprises one, two, or all of the following: (i) an LCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the LCDR1 of the anti-CD138 antibody; (ii) an LCDR2 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the LCDR2 of the anti-CD138 antibody; or (iii) an LCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the LCDR3 of the anti-CD138 antibody.

In an example, the VH comprises: (i) an HCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the HCDR1 of the anti-CD138 antibody; (ii) an HCDR2 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the HCDR2 of the anti-CD138 antibody; and (iii) an HCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the HCDR3 of the anti-CD138 antibody.

In an example, the VH comprises: (i) an HCDR1 comprising the amino acid sequence of the HCDR1 of the anti-CD138 antibody; (ii) an HCDR2 comprising the amino acid sequence of the HCDR2 of the anti-CD138 antibody; and (iii) an HCDR3 comprising the amino acid sequence of the HCDR3 of the anti-CD138 antibody.

In an example, the VL comprises: (i) an LCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the LCDR1 of the anti-CD138 antibody; (ii) an LCDR2 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the LCDR2 of the anti-CD138 antibody; and (iii) an LCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the LCDR3 of the anti-CD138 antibody.

In an example, the VL comprises: (i) an LCDR1 comprising the amino acid sequence of the LCDR1 of the anti-CD138 antibody; (ii) an LCDR2 comprising the amino acid sequence of the

LCDR2 of the anti-CD138 antibody; and (iii) an LCDR3 comprising the amino acid sequence of the LCDR3 of the anti-CD138 antibody.

In an example, the antibody molecule comprises:

(a) a VH comprising: (i) an HCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the HCDR1 of the anti-CD138 antibody; (ii) an HCDR2 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the HCDR2 of the anti-CD138 antibody; and (iii) an HCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the HCDR3 of the anti-CD138 antibody, and

(b) a VL comprising: (i) an LCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the LCDR1 of the anti-CD138 antibody; (ii) an LCDR2 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the LCDR2 of the anti-CD138 antibody; and (iii) an LCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the LCDR3 of the anti-CD138 antibody.

In an example, the antibody molecule comprises: (a) a VH comprising: (i) an HCDR1 comprising the amino acid sequence of the HCDR1 of the anti-CD138 antibody; (ii) an HCDR2 comprising the amino acid sequence of the HCDR2 of the anti-CD138 antibody; and (iii) an HCDR3 comprising the amino acid sequence of the HCDR3 of the anti-CD138 antibody, and (b) a VL comprising: (i) an LCDR1 comprising the amino acid sequence of the LCDR1 of the anti-CD138 antibody; (ii) an LCDR2 comprising the amino acid sequence of the LCDR2 of the anti-CD138 antibody; and (iii) an LCDR3 comprising the amino acid sequence of the LCDR3 of the anti-CD138 antibody.

In an example, the VH comprises an amino acid sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the VH of the anti-CD138 antibody. In an example, the antibody molecule the VH comprises the amino acid sequence of the VH of the anti-CD138 antibody.

In an example, the VL comprises an amino acid sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the VL of the anti-CD138 antibody. In an example, the VL comprises the amino acid sequence of the VL of the anti-CD138 antibody.

In an example, (a) the VH comprises an amino acid sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the VH of the anti-CD138 antibody; and (b) the VL comprises an amino acid sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues from, or has at least 85, 90, 95, 99 or 100% homology with, the amino acid sequence of the VH of the anti-CD138 antibody.

In an example, the VH comprises the amino acid sequence of the VH of the anti-CD138 antibody and the VL comprises the amino acid sequence of the VL of the anti-CD138 antibody.

In an example, the antibody molecule comprises an Fc region.

In an example, the disclosure features an antibody molecule, which competes for binding to CD138 with an anti-CD138 monoclonal antibody described herein (*e.g.*, any of antibodies CD001, CD002, CD003, CD004, CD005, CD006, 602, 603, 604, 607, 613, 614, 617, 624, 632, 616, 619, 623, 1610, 2510, 2610, 2710, 2810, 2910, or 1409).

In an example, the disclosure features an antibody molecule, which binds, or substantially binds, to an epitope that completely or partially overlaps with the epitope of an anti-CD138 monoclonal antibody described herein (*e.g.*, any of antibodies CD001, CD002, CD003, CD004, CD005, CD006, 602, 603, 604, 607, 613, 614, 617, 624, 632, 616, 619, 623, 1610, 2510, 2610, 2710, 2810, 2910, or 1409).

In an aspect, the disclosure features an antibody-molecule drug conjugate (ADC) comprising an antibody molecule described herein, optionally comprising a cytotoxic agent, further optionally comprising a linker.

In an example, the disclosure features a composition comprising an antibody molecule described herein, or an ADC described herein, optionally, wherein the composition is a pharmaceutical composition.

In an aspect, the disclosure features a composition comprising an antibody molecule described herein, or an ADC as described herein, optionally, wherein the composition is a pharmaceutical composition;

optionally wherein the composition further comprises a pharmaceutically acceptable carrier.

In an example, the composition further comprises a pharmaceutically acceptable carrier.

In an aspect, the disclosure features a nucleic acid molecule encoding a heavy chain variable region (VH), a light chain variable region (VL), or both, of an antibody molecule described herein.

In an aspect, the disclosure features a vector comprising a nucleic acid molecule described herein.

In an example, the disclosure features a cell comprising a nucleic acid molecule described herein or a vector described herein, optionally, wherein the cell is an isolated cell.

In an aspect, the disclosure features a cell comprising a nucleic acid molecule described herein or a vector described herein, wherein the cell is an isolated cell.

- 5 In an aspect, the disclosure features a kit comprising an antibody molecule described herein, an ADC described herein, or a composition described herein, and instructions to use of the antibody molecule or composition.

In an aspect, the disclosure features a container comprising an antibody molecule described herein, an ADC described herein, or a composition described herein.

In an example, the disclosure features a method of producing an anti-CD138 antibody molecule, the method comprising culturing a cell described herein under conditions that allow production of an antibody molecule, thereby producing the antibody molecule.

5 In an aspect, the disclosure features a method of producing an anti-CD138 antibody molecule, the method comprising culturing a cell described herein under conditions that allow production of an antibody molecule, thereby producing the antibody molecule; optionally wherein the method further comprises isolating or purifying the antibody molecule.

In an example, the method further comprises isolating or purifying the antibody molecule.

10 In an example, the disclosure features an antibody molecule of described herein, an ADC described herein, or a composition described herein, for use in a method of treating a cancer in a subject.

In an aspect, there is provided the use of an antibody molecule as defined herein, an ADC as defined herein or a composition as defined herein, in the manufacture of a medicament for treating a cancer in a subject.

In an example, the cancer is a hematological cancer. In an example, the cancer is a multiple myeloma. In an example, the cancer is a solid tumor, *e.g.*, a solid tumor described herein.

In an example, the antibody molecule, ADC, or composition is administered to the subject intravenously.

20 In an example, the antibody molecule, ADC, or composition is administered to the subject at a dose between 0.1 mg/kg and 50 mg/kg, between 0.2 mg/kg and 25 mg/kg, between 0.5 mg/kg and 10 mg/kg, between 0.5 mg/kg and 5 mg/kg, between 0.5 mg/kg and 3 mg/kg, between 0.5 mg/kg and 2.5 mg/kg, between 0.5 mg/kg and 2 mg/kg, between 0.5 mg/kg and 1.5 mg/kg, between 0.5 mg/kg and 1 mg/kg, between 1 mg/kg and 1.5 mg/kg, between 1 mg/kg and 2 mg/kg, between 1 mg/kg and 2.5 mg/kg, between 1 mg/kg and 3 mg/kg, between 1 mg/kg and 2.5 mg/kg, or between 1 mg/kg and 5 mg/kg.

In an example, the antibody molecule, ADC, or composition is administered to the subject at a fixed dose between 10 mg and 1000 mg, between 10 mg and 500 mg, between 10 mg and 250 mg, between 10 mg and 150 mg, between 10 mg and 100 mg, between 10 mg and 50 mg, between 250 mg and 500 mg, between 150 mg and 500 mg, between 100 mg and 500 mg, between 50 mg and 500 mg, between 25 mg and 250 mg, between 50 mg and 150 mg, between 50 mg and 100 mg, between 100 mg and 150 mg, between 100 mg and 200 mg, or between 150 mg and 250 mg.

30 In an example, the antibody molecule, ADC, or composition is administered once a week, twice a week, once every two weeks, once every three weeks, or once every four weeks.

In an example, the use further comprises determining the level of CD138 in a sample from the subject. In an example, the use further comprises administering to the subject a second therapy for cancer.

5 In an example, the disclosure features an antibody molecule described herein, an ADC described herein, or a composition described herein, for use in a method of treating a precancerous condition or preventing a cancer.

In an example, the precancerous condition is smoldering myeloma or monoclonal gammopathy of undetermined significance (MGUS). In an example, the cancer is multiple myeloma.

In an example, the disclosure features a method of causing an ADCC activity, the method comprising contacting a cell or subject an antibody molecule described herein, an ADC described herein, or a composition described herein, thereby causing the ADCC activity.

5 In an example, the disclosure features a method of treating a cancer, the method comprising administering to a subject in need thereof an effective amount of an antibody molecule described herein, an ADC described herein, or a composition described herein, thereby treating the cancer.

10 In an example, the disclosure features a method of treating a precancerous condition or preventing a cancer, the method comprising administering to a subject in need thereof an effective amount of an antibody molecule described herein, an ADC described herein, or a composition described herein, thereby treating the precancerous condition or preventing the cancer.

In an aspect, there is provided the use of an antibody as defined herein, an ADC as defined herein, or a composition as defined herein, in the manufacture of a medicament for treating a precancerous condition or preventing a cancer, optionally wherein:

- 15 (i) the precancerous condition is smoldering myeloma or monoclonal gammopathy of undetermined significance (MGUS); or
(ii) the cancer is multiple myeloma.

In an aspect, there is provided a method of detecting an anti-CD138 molecule, the method comprising contacting a cell or a subject with an antibody molecule as defined herein, thereby detecting the CD138 molecule; optionally wherein:

- 20 (i) the antibody molecule is coupled with a detectable label; and/or
(ii) the CD138 molecule is detected *in vitro*, *ex vivo*, or *in vivo*.

In an example, the disclosure features, a method of detecting an anti-CD138 molecule, the method comprising contacting a cell or a subject with an antibody molecule described herein, thereby detecting the CD138 molecule.

25 In an example, the antibody molecule is coupled with a detectable label. In an example, the CD138 molecule is detected *in vitro*, *ex vivo*, or *in vivo*.

30 The disclosure contemplates all combinations of any one or more of the foregoing aspects and/or examples, as well as combinations with any one or more of the examples set forth in the detailed description and examples.

Other features, objects, and advantages of the compositions and methods herein will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

- 5 **FIG. 1** depict an exemplary amino acid sequence of human CD138 (UniProt ID: P18827). The signal peptide includes residues 1-22 (shown in italics); the extracellular domain includes residues 23-254; the transmembrane domain includes residues 255-275; and the cytoplasmic domain includes residues 276-310. The integrin binding domain (IBD) includes residues 88-122. Known O-linked heparin sulfate chains are located at residues 37, 45 and 47 (underlined); and known O-linked chondroitin sulfate chains are located at residues 206 and 216 (underlined). A possible N-linked glycan is located at residue 43. The inferred B-B4 antibody hot spot epitope residues are Leu107, Pro108, Glu109 and Val110 (shown in bold). Exemplary peptide region that can be targeted by an anti-CD138 antibody molecules described herein includes residues Gly217 to Glu251 (shown in bold and italics). **FIG. 1** discloses SEQ ID NO: 450.
- 10
- 15 **FIG. 2** depicts the peptides used to identify anti-CD138 antibodies that bind to a desired epitope.

What is claimed is:

1. An anti-CD138 antibody molecule, which:

(i) binds to CD138 in an extracellular region proximal to the transmembrane domain of CD138;

5 wherein the C-terminus of the extracellular region proximal to the transmembrane domain is within 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain;

and/or wherein the N-terminus of the extracellular region proximal to the transmembrane domain is within 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain; and

10 (ii) causes an antibody-dependent cellular cytotoxicity (ADCC) activity on a cell expressing CD138.

2. The antibody molecule of claim 1, wherein the antibody molecule has one, two, three, or all of

15 (i)-(iv):

(i) the antibody molecule binds to an epitope on CD138 comprising five or more consecutive amino acid residues in the extracellular region;

(ii) the extracellular region proximal to the transmembrane domain comprises, or consists of, amino acids 210-250 or 220-245 of any of SEQ ID NOS: 1-3 or 450;

20 (iii) the antibody molecule binds to an Fc receptor (FcR) on the surface of an immune cell ; and/or

(iv) the cell expressing CD138 is a cancer cell or precancerous cell, optionally wherein the cancer or precancerous cell is a myeloma cell.

25 3. The antibody molecule of claim 1 or 2, which has one, two, or all of (i)-(iii):

(i) (a) does not bind, or binds with low affinity, to an extracellular region of CD138 distant from the transmembrane domain; or

(b) binds, an epitope on CD138 comprising five or more consecutive amino acid residues in an extracellular region distant from the transmembrane domain;

30 (ii) does not bind to an epitope on CD138 comprising five or more consecutive amino acid residues in an extracellular region distant from the transmembrane domain; optionally wherein:

(a) the C-terminus of the extracellular region distant from the transmembrane domain is at least 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 amino acids away from the N-terminus of the transmembrane domain; and/or

(b) the extracellular region distant from the transmembrane domain comprises amino acids 23-50, 51-95, 88-121, or 111-150 of any of SEQ ID NOS: 1-3 or 450; and/or

(iii) (a) does not bind, or binds with low affinity, to the integrin binding domain (IBD) of CD138, a region N-terminal to the IBD of CD138, or both; or (b) binds to the IBD of CD138, a region N-terminal to the IBD of CD138, or both.

4. The antibody molecule of any of claims 1-3, which has one, two, three, four, five, six, seven, eight, nine, or all of (i)-(x):

(i) binds to CD138 with a disassociation constant (K_D) of less than 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM;

(ii) the binding affinity of the antibody molecule to a membrane-bound CD138 is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 200, or 500-fold higher than the binding affinity to a soluble CD138;

(iii) binds to a membrane-bound CD138 with a K_D less than 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM;

(iv) binds to a soluble CD138 with a K_D less than 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM, or with a K_D of more than 100, 200, 300, 400, or 500 nM;

(v) binds to a membrane-bound CD138 preferably over a soluble CD138, optionally wherein the binding affinity to a membrane-bound CD138 is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold higher than the binding affinity to a soluble CD138; or binds with similar affinity to a membrane-bound CD138 and a soluble CD138, or the binding affinity to a membrane-bound CD138 is less than 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% higher than the binding affinity to a soluble CD138;

(vi) binds to C1q and causes a complement-dependent cytotoxicity (CDC) activity on a cell expressing CD138;

(vii) reduces one or more biological activities of a cell expressing CD138 *in vitro*, *ex vivo*, or *in vivo*;

(viii) mediates homotypic adhesion of one or more CD138-expressing cells;

(ix) inhibits the action of a protease on a membrane-bound CD138; and/or

(x) reduces proliferation of a cancer or precancerous cell expressing CD138.

5. The antibody molecule of any of claims 1-4, comprising:

(i) one or more heavy chain CDRs and/or one or more light chain CDRs of an anti-CD138 monoclonal antibody described herein;

5 (ii) a heavy chain variable region (VH) and/or light chain variable region (VL) of an anti-CD138 monoclonal antibody described herein; and/or

(iii) an Fc region.

6. The antibody molecule of any of claims 1-5, which comprises:

10 (i) a heavy chain variable region (VH) comprising an HCDR1 comprising an amino acid sequence of GYSFSSY (SEQ ID NO: 355); an HCDR2 comprising an amino acid sequence of HPSDST (SEQ ID NO: 351); and an HCDR3 comprising an amino acid sequence of FVY; and

(ii) a light chain variable region (VL) comprising an LCDR1 comprising an amino acid sequence of RSSKSLLYKDGKTYLN (SEQ ID NO: 352) or an LCDR1 that differs by no more than 1 amino acid residue from SEQ ID NO: 352; an LCDR2 comprising an amino acid sequence of VVSTRAS (SEQ ID NO: 353); and an LCDR3 comprising an amino acid sequence of QQLVEYPYT (SEQ ID NO: 354); optionally wherein the antibody molecule further comprises:

(iii) a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 296, or a VH region having an amino acid sequence at least 85, 90, 95, or 99% identical to SEQ ID NO: 296; or

20 (ii) a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 292, or a VL region having an amino acid sequence at least 85, 90, 95, or 99% identical to SEQ ID NO: 292.

7. The anti-CD138 antibody molecule of any of claims 1-6, which binds to an epitope on CD138 comprising four or more consecutive amino acid residues in an extracellular region proximal to the transmembrane domain of CD138.

8. The antibody molecule of claim 7, wherein the antibody molecule has one, two, three, or all of (i)-(iv):

30 (i) the C-terminus of the extracellular region proximal to the transmembrane domain is within 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain;

(ii) the N-terminus of the extracellular region proximal to the transmembrane domain is within 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, or 5 amino acids from the N-terminus of the transmembrane domain;

(iii) the extracellular region proximal to the transmembrane domain comprises, or consists of, amino acids 176-250 of any of SEQ ID NOS: 1-3 or 450; and/or

(iv) the antibody molecule does not bind, or binds with low affinity, to an extracellular region of CD138 distant from the transmembrane domain; and/or the epitope does not comprise five or more consecutive amino acid residues in an extracellular region distant from the transmembrane domain;

optionally wherein:

(a) the C-terminus of the extracellular region distant from the transmembrane domain is at least 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 amino acids away from the N-terminus of the transmembrane domain;

(b) the extracellular region distant from the transmembrane domain comprises amino acids 23-50, 51-95, 88-121, or 111-150 of any of SEQ ID NOS: 1-3 or 450; and/or

(c) the antibody molecule (1) does not bind, or binds with low affinity, to the integrin binding domain (IBD) of CD138, a region N-terminal to the IBD of CD138, or both, or (2) binds to the IBD of CD138, a region N-terminal to the IBD of CD138, or both.

9. The antibody molecule of claim 7 or 8, which:

(i) binds to an Fc receptor (FcR) on the surface of an immune cell;

(ii) is capable of causing an ADCC activity on a cell expressing CD138, optionally wherein the cell expressing CD138 is a cancer cell or precancerous cell, further optionally wherein the cancer or precancerous cell is a myeloma cell;

(iii) binds to CD138 with a disassociation constant (K_D) of less than 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM;

(iv) has a binding affinity to a membrane-bound CD138 at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 200, or 500-fold higher than the binding affinity to a soluble CD138; or which binds with similar affinity to a membrane-bound CD138 and a soluble CD138, optionally wherein the binding affinity to a membrane-bound CD138 is less than 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% higher than the binding affinity to a soluble CD138;

(v) binds to a membrane-bound CD138 with a K_D less than 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM;

(vi) binds to a soluble CD138 with a K_D of less than 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 8, 6, 4, 3, 2, 1, 0.5, 0.2, 0.1, 0.05, 0.01, 0.005, or 0.001 nM, or 10-0.001, 10-0.01, 5-0.01, 3-0.05, or 1-0.1 nM, or greater than 100, 200, 300, 400, or 500 nM;

(vii) (a) binds to a membrane-bound CD138 preferably over a soluble CD138, optionally wherein the binding affinity to a membrane-bound CD138 is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold higher than the binding affinity to a soluble CD138; or (b) binds to C1q and causes a complement-dependent cytotoxicity (CDC) activity on a cell expressing CD138;

(viii) reduces one or more biological activities of a cell expressing CD138 *in vitro*, *ex vivo*, or *in vivo*;

(ix) mediates homotypic adhesion of one or more CD138-expressing cells;

(x) inhibits the action of a protease on a membrane-bound CD138;

(xi) reduces proliferation of a cancer or precancerous cell expressing CD138;

(xii) comprises one or more heavy chain CDRs and/or one or more light chain CDRs of an anti-CD138 monoclonal antibody described herein;

(xiii) comprises a heavy chain variable region (VH) and/or light chain variable region (VL) of an anti-CD138 monoclonal antibody described herein; and/or

(xiv) comprises an Fc region.

10. The anti-CD138 antibody molecule of any of claims 1-9, which comprises one or both of:

(a) a heavy chain variable region (VH), wherein the VH comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3), wherein the VH comprises one, two, or all of the following:

(i) an HCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the HCDR1 of any of antibodies CD001, CD002, CD003, CD004, CD005, CD006, 602, 603, 604, 607, 613, 614, 617, 624, 632, 616, 619, 623, 1610, 2510, 2610, 2710, 2810, 2910, or 1409;

(ii) an HCDR2 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the HCDR2 of the anti-CD138 antibody; or

(iii) an HCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the HCDR3 of the anti-CD138 antibody; or

(b) a light chain variable region (VL), wherein the VL comprises three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), wherein the VL comprises one, two, or all of the following:

(i) an LCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the LCDR1 of the anti-CD138 antibody;

(ii) an LCDR2 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the LCDR2 of the anti-CD138 antibody; or

(iii) an LCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the LCDR3 of the anti-CD138 antibody.

11. The antibody molecule of claim 10, wherein the antibody molecule has one, two, or all of (I), (II) and (III):

(I) wherein the antibody molecule has (a), (b) or both (a) and (b):

(a) the VH comprises:

(i) an HCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the HCDR1 of the anti-CD138 antibody;

(ii) an HCDR2 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the HCDR2 of the anti-CD138 antibody; and

(iii) an HCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the HCDR3 of the anti-CD138 antibody;

optionally wherein the VH comprises: (i) an HCDR1 comprising the amino acid sequence of the HCDR1 of the anti-CD138 antibody; (ii) an HCDR2 comprising the amino acid sequence of the HCDR2 of the anti-CD138 antibody; and (iii) an HCDR3 comprising the amino acid sequence of the HCDR3 of the anti-CD138 antibody; or

(b) the VL comprises:

(i) an LCDR1 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the LCDR1 of the anti-CD138 antibody;

(ii) an LCDR2 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the LCDR2 of the anti-CD138 antibody; and

(iii) an LCDR3 comprising an amino acid sequence that differs by no more than 1, 2, or 3 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the LCDR3 of the anti-CD138 antibody;

optionally wherein the VL comprises: (i) an LCDR1 comprising the amino acid sequence of the LCDR1 of the anti-CD138 antibody; (ii) an LCDR2 comprising the amino acid sequence of the LCDR2 of the anti-CD138 antibody; and (iii) an LCDR3 comprising the amino acid sequence of the LCDR3 of the anti-CD138 antibody;

(II) wherein the antibody molecule has (a), (b), or both (a) and (b):

(a) the VH comprises an amino acid sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the VH of the anti-CD138 antibody;

optionally wherein the VH comprises the amino acid sequence of the VH of the anti-CD138 antibody; or

(b) the VL comprises an amino acid sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues from, or has at least 85, 90, 95, 99 or 100% sequence identity with, the amino acid sequence of the VL of the anti-CD138 antibody;

optionally wherein the VL comprises the amino acid sequence of the VL of the anti-CD138 antibody; and/or

(III) the antibody molecule comprises an Fc region.

12. The anti-CD138 antibody molecule of any of claims 1-11, which comprises:

(I) (a) a heavy chain variable region (VH), wherein the VH comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3), wherein the VH comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3), wherein the VH comprises: (i) an HCDR1 comprising an amino acid sequence of G-Y-N/S/T-F-S-S-Y (SEQ ID NO: 438); (ii) an HCDR2 comprising an amino acid sequence of H-P-S-D-S-T (SEQ ID NO: 351); or (iii) an HCDR3 comprising an amino acid sequence of F-V-Y; and (b) a light chain variable region (VL), wherein the VL comprises three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), wherein the VL comprises one, two, or all of: (i) an LCDR1 comprising an amino acid sequence of R-S-S-K-S-L-L-Y-K-D-G-K-T-Y-L-N (SEQ ID NO: 352); (ii) an LCDR2 comprising an amino acid

sequence of V-V-S-T-R-A-S (SEQ ID NO: 353); or (iii) an LCDR3 comprising an amino acid sequence of Q-Q-L-V-E-Y-P-Y-T (SEQ ID NO: 354); or

(II) (a) a heavy chain variable region (VH), wherein the VH comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3), wherein the VH comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3), wherein the VH comprises: (i) an HCDR1 comprising an amino acid sequence of S-Y-Y-M-H (SEQ ID NO: 380); (ii) an HCDR2 comprising an amino acid sequence of T-I-H-P-S-D-S-T-T-N-C/Y-N-Q-K-F-K-G (SEQ ID NO: 439); or (iii) an HCDR3 comprising an amino acid sequence of F-V-Y; and (b) a light chain variable region (VL), wherein the VL comprises three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3), wherein the VL comprises one, two, or all of: (i) an LCDR1 comprising an amino acid sequence of R-S-S-K-S-L-L-Y-K-D-G-K-T-Y-L-N (SEQ ID NO: 352); (ii) an LCDR2 comprising an amino acid sequence of V-V-S-T-R-A-S (SEQ ID NO: 353); or (iii) an LCDR3 comprising an amino acid sequence of Q-Q-L-V-E-Y-P-Y-T (SEQ ID NO: 354).

13. The antibody molecule of any of claims 1-12, which has one, two, three, four, five, six, seven, eight, nine, or all of (i)-(x):

- (i) comprises two VHs and two VLs;
- (ii) is a synthetic antibody molecule or an isolated antibody molecule;
- (iii) is a monovalent antibody molecule, a multivalent antibody molecule, a monospecific molecule, or a multispecific antibody molecule;
- (iv) is a humanized antibody molecule;
- (v) comprises one or more framework regions derived from human framework germline sequence;
- (vi) is an IgG antibody;
- (vii) comprises a heavy chain constant region of IgG chosen from IgG1, IgG2, IgG3, or IgG4;
- (viii) comprises a light chain constant region of kappa or lambda light chain;
- (ix) comprises an Fc region comprising one or more mutations to increase the binding affinity to neonatal receptor FcRn and/or the half-life of the antibody molecule; and/or
- (x) comprises an Fc region comprising one or more mutations increase one or more of half-life, ADCC, CDC, or ADCP.

14. The antibody molecule of any of claims 1-13, which competes for binding to CD138 with any of antibodies CD001, CD002, CD003, CD004, CD005, CD006, 602, 603, 604, 607, 613, 614, 617, 624, 632, 616, 619, 623, 1610, 2510, 2610, 2710, 2810, 2910, or 1409.

15. The antibody molecule of any of claims 1-13, which binds to an epitope that completely or partially overlaps with the epitope of any of antibodies CD001, CD002, CD003, CD004, CD005, CD006, 602, 603, 604, 607, 613, 614, 617, 624, 632, 616, 619, 623, 1610, 2510, 2610, 2710, 2810, 2910, or 1409.

16. An antibody-molecule drug conjugate (ADC) comprising an antibody molecule of any of claims 1-15, optionally comprising a cytotoxic agent, further optionally comprising a linker.

17. A composition comprising an antibody molecule of any of claims 1-15, or an ADC of claim 16, optionally, wherein the composition is a pharmaceutical composition; optionally wherein the composition further comprises a pharmaceutically acceptable carrier.

18. A nucleic acid molecule encoding a heavy chain variable region (VH), a light chain variable region (VL), or both, of an antibody molecule of any of claims 1-15.

19. A vector comprising a nucleic acid molecule of claim 18.

20. A cell comprising a nucleic acid molecule of claim 18 or a vector of claim 19, optionally, wherein the cell is an isolated cell.

21. A kit comprising an antibody molecule of any of claims 1-15, an ADC of claim 16, or a composition of claim 17, and instructions for use of the antibody molecule or composition.

22. A container comprising an antibody molecule of any of claims 1-15, an ADC of claim 16, or a composition of claim 17.

23. A method of producing an anti-CD138 antibody molecule, the method comprising culturing a cell of claim 20 under conditions that allow production of an antibody molecule, thereby producing the antibody molecule; optionally wherein the method further comprises isolating or purifying the antibody molecule.

24. Use of an antibody molecule of any of claims 1-15, an ADC of claim 16, or a composition of claim 17, in the manufacture of a medicament for treating a cancer in a subject.

25. The use of claim 24, wherein the use has one, two, three, four, five, six, or all of (i)-(vii):

(i) the cancer is a hematological cancer, a multiple myeloma, and/or a solid tumor;

(ii) the antibody molecule, ADC, or composition is to be administered to the subject intravenously;

(iii) the antibody molecule, ADC, or composition is to be administered to the subject at a dose between 0.1 mg/kg and 50 mg/kg, between 0.2 mg/kg and 25 mg/kg, between 0.5 mg/kg and 10 mg/kg, between 0.5 mg/kg and 5 mg/kg, between 0.5 mg/kg and 3 mg/kg, between 0.5 mg/kg and 2.5 mg/kg, between 0.5 mg/kg and 2 mg/kg, between 0.5 mg/kg and 1.5 mg/kg, between 0.5 mg/kg and 1 mg/kg, between 1 mg/kg and 1.5 mg/kg, between 1 mg/kg and 2 mg/kg, between 1 mg/kg and 2.5 mg/kg, between 1 mg/kg and 3 mg/kg, between 1 mg/kg and 2.5 mg/kg, or between 1 mg/kg and 5 mg/kg;

(iv) the antibody molecule, ADC, or composition is to be administered to the subject at a fixed dose between 10 mg and 1000 mg, between 10 mg and 500 mg, between 10 mg and 250 mg, between 10 mg and 150 mg, between 10 mg and 100 mg, between 10 mg and 50 mg, between 250 mg and 500 mg, between 150 mg and 500 mg, between 100 mg and 500 mg, between 50 mg and 500 mg, between 25 mg and 250 mg, between 50 mg and 150 mg, between 50 mg and 100 mg, between 100 mg and 150 mg.

between 100 mg and 200 mg, or between 150 mg and 250 mg;

(v) wherein the antibody molecule, ADC, or composition is to be administered once a week, twice a week, once every two weeks, once every three weeks, or once every four weeks;

(vi) wherein the use further comprises determining the level of CD138 in a sample from the subject; and/or

(vii) wherein the use further comprises a second therapy for cancer to be administered to the subject.

26. Use of an antibody molecule of any of claims 1-15 an ADC of claim 16, or a composition of claim 17, in the manufacture of a medicament for treating a precancerous condition or preventing a cancer, optionally wherein:

(i) the precancerous condition is smoldering myeloma or monoclonal gammopathy of undetermined significance (MGUS); or

(ii) the cancer is multiple myeloma.

27. A method of detecting an anti-CD138 molecule, the method comprising contacting a cell or a subject with an antibody molecule of any of claims 1-15, thereby detecting the CD138 molecule; optionally wherein:

(i) the antibody molecule is coupled with a detectable label; and/or

5 (ii) the CD138 molecule is detected *in vitro*, *ex vivo*, or *in vivo*.